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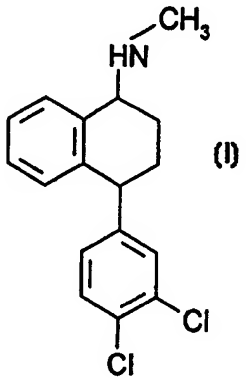
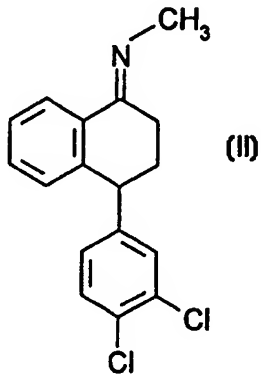


(I)



(II)

(57) Abstract

The invention relates to a process for the preparation of cis–(1R, 1S)–N–methyl–4–(3,4–dichlorophenyl)–1,2,3,4–tetrahydro–1–naphthalene–1–amine of formula (I) and pharmaceutically acceptable acid addition salts thereof by reducing (±)–4–(S,R)–[(3,4–dichlorophenyl)–3,4–dihydro–1(2H)–naphthalene–1–ylidene]–methylamine of formula (II) in the presence of a palladium catalyst and if desired converting the base of formula (I) obtained into a pharmaceutically acceptable acid addition salt thereof which comprises using a palladium catalyst applied on a carrier, containing 5–30 % by weight of palladium and pre–treated with an alkali halide. The compound of formula (I) is a useful pharmaceutical active ingredient.

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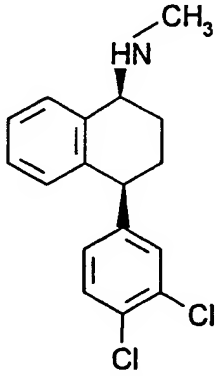
PROCESS FOR THE PREPARATION OF SERTRALINE AND ITS 1,R-STEREOISOMER

Background of the invention

The invention relates to a new and improved process for the preparation of a pharmaceutical active ingredient. More particularly it is concerned with a process for the preparation of cis-(1R,1S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalene-1-amine and pharmaceutically acceptable acid addition salts thereof.

State of the prior art

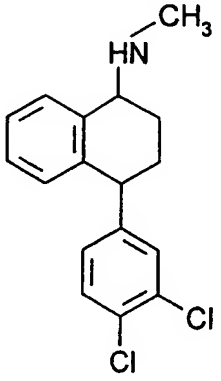
Cis-(1S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalene-1-amine-hydrochloride of the Formula



Ia
cis-1S

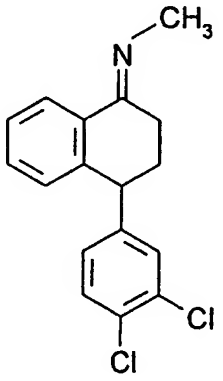
is a medicine useful against mental depression having the INN sertraline. The chemical nomenclature of sertraline is cis-(1S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalene-amine.

According to prior art the compound of the Formula



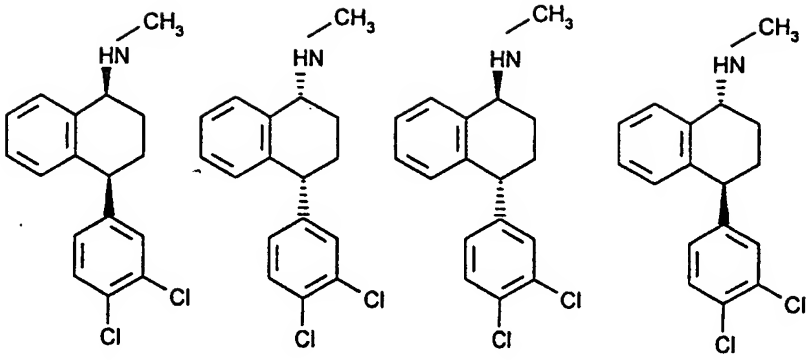
I

may be prepared by reduction of (±)-4-(S,R)-[(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalene-1-ylidene]-methylamine of the Formula



II

The compound of the Formula I contains two asymmetrical centres and may be present in the form of 4 stereoisomers. These correspond to the Formulae Ia-Id:



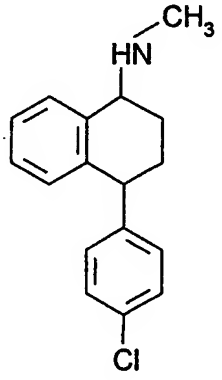
Ia cis-1S | Ib cis-1R | Ic trans-1S | Id trans-1R

According to prior art the reduction of the compound of the Formula II can be performed in toluene as medium with sodium borohydride [Welch, W.M. tsai: J. Med. Chem. 27, 1508 (1984)]. The borohydride reduction gives a 1:1 diastereomeric mixture of the cis 1S,1R [Ia and Ib] and the trans 1S,1R [Ic and Id] diastereomers, which can be separated by means of chromatography.

According to EP 30081 sertraline can be prepared from the cis-(1R) and cis-(1S) enantiomer mixture. From the enantiomer mixture salts are formed with R-amygdalic acid, whereby the R-amygdelate salt of the cis-(1S)-enantiomer precipitates and the R-amygdelate salt of the cis-(1R)-enantiomer remains in the solution. From the amygdelate salt of the cis-(1S)-enantiomer prepared in pure form the base is set free with alkali and the hydrochloride of the cis-(1S)-stereoisomer (sertraline) is formed with hydrochloric acid.

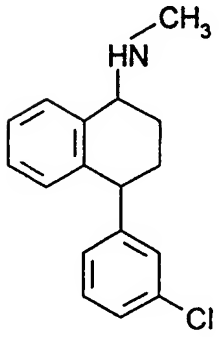
According to US patent No. 4,536,518 the compound of the Formula II is reduced with molecular hydrogen in the

presence of a 10 % palladium-charcoal catalyst at atmospheric pressure in tetrahydrofurane as medium. According to the disclosure of the patent specification the reaction is diastereoselective and the isomeric ratio of the cis and trans isomers amounts to 70:30. Because the sertraline end product is a cis isomer, it is desirable to achieve a cis/trans isomer ratio as high as possible. Sertraline is isolated by separating the cis-racemate obtained. On reproducing the process disclosed in US patent No. 4,536,518 we have found that in the reaction in addition to the stereoisomers of the Formulae Ia-Id also the monochloro compounds of the Formulae



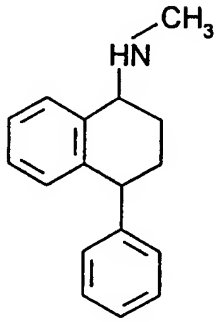
III

and



IV

are formed in an amount of about 8 % and the dechloro compound of the Formula



V

is formed in an amount of about 3 %. The separation of these by-products is circumstantial on the one hand and decreases the yield of the desired compound on the other. Thus the chemical selectivity of the reaction is lower.

Summary of the invention

It is the object of the invention to eliminate the drawbacks of the known methods, to provide a higher cis/trans stereoisomer ratio than by the known procedures and to suppress the formation of by-products.

The above object is solved by means of the process of the present invention.

According to the process of the present invention there is provided a process for the preparation of cis-(1R,1S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalene-1-amine of the Formula I (Ia and Ib) and pharmaceutically acceptable acid addition salts thereof by reducing (±)-4-(S,R)-[(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalene-1-ylidene]-methylamine of the Formula II in the presence of a palladium

catalyst and if desired converting the base of the Formula I (Ia and Ib) obtained into a pharmaceutically acceptable acid addition salt thereof which comprises using a palladium catalyst applied on a carrier, containing 5-30 % by weight of palladium and pre-treated with an alkali halide.

Detailed description of the invention

The present invention is based on the recognition that the diastereoselectivity of the reaction can be significantly improved by carrying out catalytic hydrogenation of the compound of the Formula II in the presence of a palladium catalyst pre-treated according to the present invention. The process of the present invention gives a cis/trans ratio of 85-95/15-5 (in %).

The present invention is based on the further recognition that when carrying out hydrogenation of the compound of the Formula II in the presence of a palladium-catalyst pre-treated according to the present invention the formation of the by-products of the Formulae III, IV and V is suppressed. On carrying out catalytic hydrogenation according to the process of the present invention the total amount of said contaminating by-products in the reaction mixture is below 0.5 %.

The catalyst used according to the process of the present invention is a palladium catalyst applied onto a carrier containing preferably 5-30 % by weight of palladium related to dry carrier. As palladium carrier charcoal or barium sulfate, preferably charcoal may be used.

The palladium-charcoal catalyst is pre-treated preferably with a potassium halide or sodium halide. One may use preferably potassium chloride, potassium bromide, potassium fluoride, potassium iodide or sodium iodide. Said alkali halide may be used in an amount of 0.005-5 g, preferably 0.05-0.5 g, related to 1 g of palladium.

The alkali halide may be used preferably in the form of a solution formed with a lower alkanol, water or a mixture thereof. As lower alkanol straight or branched chain alkanols having 1-4 carbon atoms may be used (e.g. methanol, ethanol, n-propanol, isopropanol or n-butanol). According to particularly preferred embodiment of our invention the alkali halide is used in the form of a solution formed with water or a mixture of water and methanol, or water and ethanol.

According to a preferred embodiment of the process of the present invention the catalyst is pre-treated in the presence of (±)-4-(S,R)-[(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalene-1-ylidene]-methylamine starting material. According to this embodiment one may proceed preferably by adding to the solution of the (±)-4-(S,R)-[(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalene-1-ylidene]-methylamine starting material at first the aqueous-alkanolic solution of the alkali halide and thereafter the catalyst. According to a variant of this process the palladium catalyst is at first pre-treated with the solution containing the alkali halide and is thereafter added to the reaction mixture.

As solvent of (±)-4-(S,R)-[(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalene-1-ylidene]-methylamine and reaction medium polar protic or aprotic solvents may be used. As reaction medium ethers (e.g. tetrahydrofurane, dioxane, diethyl ether), lower alkyl esters (e.g. ethyl acetate), chlorinated hydrocarbons (e.g. dichloro methane, chloroform) or lower alkanols (e.g. methanol, ethanol etc.) may be used. Tetrahydrofurane, ethanol, dichloro methane or ethyl acetate may particularly preferably serve as reaction medium.

The reaction may be carried out at a temperature of 0-150°C, preferably at 10-100°C.

Hydrogenation may be performed under a pressure of 1-25 atm, preferably at 1-10 atm.

According to a preferred embodiment of our invention the process may be carried out as follows:

The (±)-4-(S,R)-[(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalene-1-ylidene]-methylamine starting material is dissolved in ethanol, tetrahydrofurane, dichloro methane or ethyl acetate, whereupon a solution of the alkali halide formed with a mixture of water and methanol or water and ethanol is added and thereafter the palladium-charcoal catalyst is added. Hydrogenation is carried out under stirring, preferably at room temperature and atmospheric pressure.

The reaction time may be determined by preliminary experiments, depending on the stirring.

The reaction mixture may be worked up by different methods. One may preferably proceed by removing the

catalyst by filtration or centrifugation, and thereafter precipitating the desired pharmaceutically acceptable salt from the filtrate containing the bases of the Formulae Ia-Id by adding the corresponding acid and isolating said precipitated salt by filtration or centrifuging.

According to a preferred embodiment of our process the hydrochloride is precipitated by means of treatment with hydrochloric acid. However other pharmaceutically acceptable salts (e.g. sulfate, nitrate, phosphate, acetate, tartarate, maleate, fumarate, succinate) may be prepared too.

Salt formation may be carried out by methods known per se.

The process of the present invention has the following advantages:

– in the compound of the Formula I obtained the cis/trans ratio is very favourable; the desired cis-isomers are formed in a higher ratio than by the known methods;

– the amount of the monochloro- and dechloro-derivatives is reduced; the formation of the undesired by-products is suppressed;

– a cis (±)racemate of high purity is obtained;

– from the cis(±)racemate formed highly pure sertraline end-product can be very easily prepared.

Further details of the present invention are to be found in the Examples without limiting the scope of protection to said working Examples.

Example 1

To a solution of 10 g of (±)-4-(S,R)-[(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalene-1-ylidene]-methylamine and 120 ml of tetrahydrofurane 7.5 ml of a 1:1 mixture of water and methanol containing 60 mg of potassium chloride are added. Thereafter 1 g of a palladium catalyst is added (palladium content 8 %; carbon content 28 %; water content 64 %). The reaction mixture is flushed with nitrogen under stirring and hydrogenated at room temperature under atmospheric pressure. Hydrogenation is continued until the imine starting material in the reaction mixture is consumed.

Hydrogenation having been completed the catalyst is filtered off and the filtrate is acidified at room temperature with concentrated aqueous hydrochloric acid. The precipitated product is filtered. Thus 10.3 g of cis-(1R,1S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalene-1-amine-hydrochloride are obtained. Yield 91 %, mp.: 280-283°C.

Example 2

To a solution of 10 g of (±)-4-(S,R)-[(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalene-1-ylidene]-methylamine and 200 ml of ethanol 20 ml of a 1:1 mixture of water and ethanol containing 60 mg of potassium chloride are added. Thereafter 0.85 g of a palladium catalyst is added (palladium content 8 %; carbon content 28 %; water content 64 %). The reaction mixture is flushed with nitrogen under stirring and hydrogenated at room temperature under atmospheric

pressure. Hydrogenation is continued until the imine starting material in the reaction mixture is consumed.

Hydrogenation having been completed the catalyst is filtered off and the filtrate is acidified at room temperature with concentrated aqueous hydrochloric acid. The precipitated product is filtered and recrystallized from a mixture of methanol and water. Thus 8.25 g of cis-(1R,1S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalene-1-amine-hydrochloride are obtained. Yield 74 %, mp.: 282-285°C.

Example 3

To a solution of 10 g of (±)-4-(S,R)-[(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalene-1-ylidene]-methylamine and 150 ml of ethyl acetate 15 ml of a 1:1 mixture of water and methanol containing 60 mg of potassium chloride are added. Thereafter 1 g of a palladium catalyst is added (palladium content 8 %; carbon content 28 %; water content 64 %). The reaction mixture is flushed with nitrogen under stirring and hydrogenated at room temperature under atmospheric pressure. Hydrogenation is continued until the imine starting material in the reaction mixture is consumed.

Hydrogenation having been completed the catalyst is filtered off and the filtrate is acidified at room temperature with concentrated aqueous hydrochloric acid. The precipitated product is filtered and recrystallized from a mixture of methanol and water. Thus 7.58 g of (±)-4-(S,R)-[(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalene-1-ylidene]-methylamine are obtained. Yield 68 %, mp.: 282-285°C.

Example 4

To a solution of 10 g of (±)-4-(S,R)-[(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalene-1-ylidene]-methylamine and 150 ml of tetrahydrofurane 9 ml of a 1:1 mixture of water and methanol containing 23 mg of potassium chloride are added. Thereafter 1 g of a palladium catalyst is added (palladium content 8 %; carbon content 28 %; water content 64 %). The reaction mixture is flushed with nitrogen under stirring and hydrogenated at room temperature under atmospheric pressure. Hydrogenation is continued until the imine starting material in the reaction mixture is consumed.

Hydrogenation having been completed the catalyst is filtered off and the filtrate is acidified at room temperature with concentrated aqueous hydrochloric acid. The precipitated product is filtered and recrystallized from a mixture of methanol and water. Thus 8.83 g of cis-(1R,1S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalene-1-amine-hydrochloride are obtained. Yield 79 %, mp.: 282-285°C.

Example 5

To a solution of 10 g of (±)-4-(S,R)-[(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalene-1-ylidene]-methylamine and 150 ml of tetrahydrofurane 10 ml of a 1:1 mixture of water and methanol containing 50 mg of potassium fluoride and 1.0 g of a palladium-charcoal catalyst are added (palladium content 8 %; carbon content 28 %; water content 64 %). The reaction mixture is flushed with nitrogen under stirring and hydrogenated at room temperature under atmospheric

pressure. Hydrogenation is continued until the imine starting material in the reaction mixture is consumed.

Hydrogenation having been completed the catalyst is filtered off and the filtrate is acidified at room temperature with concentrated aqueous hydrochloric acid. The precipitated product is filtered and recrystallized from a mixture of methanol and water. Thus 7.38 g of cis-(1R,1S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalene-1-amine-hydrochloride are obtained. Yield 66 %, mp.: 282-285°C.

Example 6

To a solution of 10 g of (±)-4-(S,R)-[(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalene-1-ylidene]-methylamine and 150 ml of tetrahydrofurane 1.5 ml of a 1:1 mixture of water and methanol containing 24 mg of sodium iodide and 1.0 g of a palladium-charcoal catalyst are added (palladium content 8 %; carbon content 28 %; water content 64 %). The reaction mixture is flushed with nitrogen under stirring and hydrogenated at room temperature under atmospheric pressure. Hydrogenation is continued until the imine starting material in the reaction mixture is consumed.

Hydrogenation having been completed the catalyst is filtered off and the filtrate is acidified at room temperature with concentrated aqueous hydrochloric acid. The precipitated product is filtered. Thus 9.28 g of cis-(1R,1S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalene-1-amine-hydrochloride are obtained. Yield 83 %, mp.: 280-283°C.

Example 7

To a solution of 10 g of (±)-4-(S,R)-[(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalene-1-ylidene]-methylamine and 150 ml of ethanol 1.5 ml of a 1:1 mixture of water and methanol containing 27 mg of potassium iodide and 1.0 g of a palladium-charcoal catalyst are added (palladium content 8 %; carbon content 28 %; water content 64 %). The reaction mixture is flushed with nitrogen under stirring and hydrogenated at room temperature under atmospheric pressure. Hydrogenation is continued until the imine starting material in the reaction mixture is consumed.

Hydrogenation having been completed the catalyst is filtered off and the filtrate is acidified at room temperature with concentrated aqueous hydrochloric acid. The precipitated product is filtered and recrystallized from a mixture of methanol and water. Thus 8.04 g of cis-(1R,1S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalene-1-amine-hydrochloride are obtained. Yield 72.1 %, mp.: 282-285°C.

Example 8

To a solution of 10 g of (±)-4-(S,R)-[(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalene-1-ylidene]-methylamine and 175 ml of tetrahydrofurane 0.5 ml of a 1:1 mixture of water and methanol containing 9 ml of potassium iodide and 1.0 g of a palladium-charcoal catalyst are added (palladium content 8 %; carbon content 28 %; water content 64 %). The reaction mixture is flushed with nitrogen under stirring and hydrogenated at room temperature under a pressure of 3 bar.

Hydrogenation is continued until the imine starting material in the reaction mixture is consumed.

Hydrogenation having been completed the catalyst is filtered off and the filtrate is acidified at room temperature with concentrated aqueous hydrochloric acid. The precipitated product is filtered. Thus 10.3 g of cis-(1R,1S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalene-1-amine-hydrochloride are obtained. Yield 91 %, mp.: 280-283°C.

Example 9

To a solution of 10 g of (±)-4-(S,R)-[(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalene-1-ylidene]-methylamine and 150 ml of ethyl acetate 1.5 ml of a 1:1 mixture of water and methanol containing 27 mg of potassium iodide and 1.0 g of a palladium-charcoal catalyst are added (palladium content 8 %; carbon content 28 %; water content 64 %). The reaction mixture is flushed with nitrogen under stirring and hydrogenated at room temperature under atmospheric pressure. Hydrogenation is continued until the imine starting material in the reaction mixture is consumed.

Hydrogenation having been completed the catalyst is filtered off and the filtrate is acidified at room temperature with concentrated aqueous hydrochloric acid. The precipitated product is filtered and recrystallized from a mixture of methanol and water. Thus 6.91 g of cis-(1R,1S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalene-1-amine-hydrochloride are obtained. Yield 62 %, mp.: 282-285°C.

Example 10

To a solution of 10 g of (±)-4-(S,R)-[(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalene-1-ylidene]-methylamine and 150 ml of tetrahydrofurane 1.5 ml of a 1:1 mixture of water and methanol containing 27 mg of potassium iodide, 1.5 ml of a 1:1 mixture of water and methanol containing 12 mg of potassium chloride and 1.0 g of a palladium-charcoal catalyst are added (palladium content 8 %; carbon content 28 %; water content 64 %). The reaction mixture is flushed with nitrogen under stirring and hydrogenated at room temperature under atmospheric pressure. Hydrogenation is continued until the imine starting material in the reaction mixture is consumed.

Hydrogenation having been completed the catalyst is filtered off and the filtrate is acidified at room temperature with concentrated aqueous hydrochloric acid. The precipitated product is filtered and recrystallized from a mixture of methanol and water. Thus 10.3 g of cis-(1R,1S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalene-1-amine-hydrochloride are obtained. Yield 91 %, mp.: 282-285°C.

Example 11

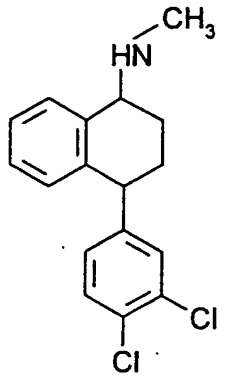
To a solution of 10 g of (±)-4-(S,R)-[(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalene-1-ylidene]-methylamine and 175 ml of tetrahydrofurane 0.5 ml of a 1:1 mixture of water and methanol containing 10 mg of potassium iodide and 1.0 g of a palladium-charcoal catalyst are added (palladium content 8 %; carbon content 28 %; water content 64 %). The reaction mixture is flushed with nitrogen under stirring and

hydrogenated at 80°C and under a pressure of 8 bar. Hydrogenation is continued until the imine starting material in the reaction mixture is consumed.

Hydrogenation having been completed the catalyst is filtered off and the filtrate is acidified at room temperature with concentrated aqueous hydrochloric acid. The precipitated product is filtered. Thus 10.3 g of cis-(1R,1S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalene-1-amine-hydrochloride are obtained. Yield 91 %, mp.: 280-283°C.

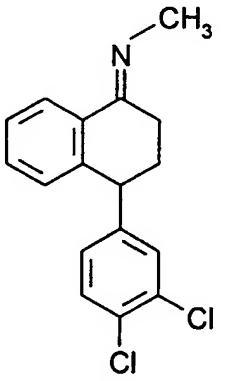
What we claim is,

1. Process for the preparation of cis-(1R,1S)-N-methyl-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-1-naphthalene-1-amine of the Formula



I

and pharmaceutically acceptable acid addition salts thereof by reducing (±)-4-(S,R)-[(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalene-1-ylidene]-methylamine of the Formula



II

in the presence of a palladium catalyst and if desired converting the base of the Formula I obtained into a pharmaceutically acceptable acid addition salt thereof which comprises using a palladium catalyst applied on a carrier, containing 5-30 % by weight of palladium and pre-treated with an alkali halide.

2. Process according to Claim 1 which comprises using a palladium catalyst pre-treated with potassium chloride, potassium fluoride, potassium iodide or sodium iodide or a mixture thereof, preferably with potassium chloride or potassium iodide or a mixture thereof.

3. Process according to any of Claims 1 and 2 which comprises carrying out pre-treatment of the palladium catalyst in water or a polar solvent or a mixture thereof, preferably in a methanolic-aqueous medium.

4. Process according to any of Claims 1-3 which comprises carrying out pre-treatment of the palladium catalyst with an alkali halide in the presence of (±)-4-(S,R)-[(3,4-dichlorophenyl)-3,4-dihydro-1(2H)-naphthalene-1-ylidene]-methylamine of the Formula II.

5. Process according to any of Claims 1-4 which comprises carrying out catalytic hydrogenation in a polar protic or aprotic solvent.

6. Process according to Claim 5 which comprises using as solvent an ether, preferably tetrahydrofurane; a lower alkyl ester, preferably ethyl acetate or a lower alkanol, preferably ethanol.

7. Process according to any of Claims 1-6 which comprises carrying out hydrogenation at 0-150°C, preferably at 10-100°C.

8. Process according to any of Claims 1-7 which comprises carrying out hydrogenation at a pressure of 1-25 atm, preferably under a pressure of 1-10 atm.

INTERNATIONAL SEARCH REPORT

.national Application No
PCT/HU 99/00036

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C209/52 C07C211/42

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 536 518 A (WELCH JR WILLARD M ET AL) 20 August 1985 (1985-08-20) cited in the application column 10, line 11-19 column 12, line 12-21	1-8

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 July 1999	30/07/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Goetz, G

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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PCT/HU 99/00036

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